

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Valerie Legrand et al.

Application No.: 10/826,690

Confirmation No.: 9585

Filed: April 19, 2004

Art Unit: 1618

For: MICROPARTICULATE ORAL GALENICAL
FORM FOR THE DELAYED AND
CONTROLLED RELEASE OF
PHARMACEUTICAL ACTIVE PRINCIPLES

Examiner: L. Schlientz

DECLARATION OF CATHERINE CASTAN

1. My name is Catherine CASTAN.
2. I have been an employee of Flamel Technologies, S.A. since 1992.
3. My position at Flamel Technologies, S.A. is Director of Galenic Department.
4. I have a Ph.D. in Polymer Chemistry.
5. I have worked in the area of pharmaceutical compositions for 21 years.
6. I consider myself to be one of skill in the art of oral pharmaceutical compositions for delayed and controlled release of active principles.
7. I reviewed the office action that issued on September 15, 2009, for U.S. Application No. 10/826,690.
8. I also reviewed EP 1101490 ("Ishibashi"), a reference cited by the Examiner in a 35 U.S.C. § 112, first paragraph, rejection.
9. I believe the Examiner is alleging that Ishibashi has formulations that meet all of the characteristics of Applicant's formulations but do not have the claimed functional dissolution properties. *See*, Office Action at pages 5-6.
10. As one of skill in the art, I believe Ishibashi does not teach the claimed composition. Specifically, Ishibashi does not teach the very small size range of about 200 to about 800 microns.

11. The structure of the coated granules described in Ishibashi is depicted in figure 1 below. A thick layer containing the drug substance is deposited onto an inert carrier of diameter R0 ("nonpareil"). This granule is covered by a coating that controls the release of the drug.

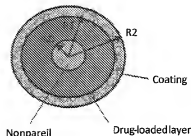


FIGURE 1

12. Below I calculated the lower limit of the Ishibashi coated granules particle size, and show that the lower limit of Ishibashi are greater than the particle diameters claimed in this application.

13. The calculations are based on elementary geometric considerations justified by the spherical shape of the inert carrier (*see* Ishibashi, page 9, [0060]), and from the data disclosed in the examples of Ishibashi.

14. Ishibashi, however, does not disclose all of the information necessary to calculate the particle size of the coated granules. It does not disclose the size of the Nonpareil 103 and it does not disclose the concentration of the sucrose solution that was used.

15. Concerning the Nonpareil 103 particle size, the Handbook of Pharmaceutical Excipients, Pharmaceutical Press, second edition (1994) and third edition (2000) (*see* Appendix) states that at the time of patent application Ishibashi the following particle sizes were available:

"Particle size distribution: sugar spheres are of a uniform diameter.
The following sizes are commercially available (US standard sieves):

35-40 mesh (450-500 μ m)
30-35 mesh (500-590 μ m)
25-30 mesh (590-710 μ m)
20-25 mesh (710-840 μ m)
18-20 mesh (840-1000 μ m)
16-20 mesh (840-1190 μ m)
14-18 mesh (1000-1410 μ m)"

Therefore, to calculate the smallest size of coated granules that Ishibashi could have manufactured, I considered that he used the smallest available nonpareil 103, i.e. 35-40 mesh (425-500 μm).

16. To calculate the smallest size of coated granules according to Ishibashi, first set the following variables:

- a. M_0 is the mass (in kg) of the neutral beads with specific weight ρ_0 (in kg/m^3)
- b. R_0 is the radius of the inert carrier (in m)
- c. M_1 is the mass of active plus additives deposited onto the inert layer and ρ_1 the specific mass (in kg/m^3) of this drug loaded layer
- d. R_1 is the radius of the drug containing granule (in m)
- e. M_2 is the mass of coating with a specific weight ρ_2 (kg/m^3). M_2 is deduced from the mass fraction $M_2/(M_0+M_1)$ given by Ishibashi, and
- f. R_2 is the radius of the coated granule (in m).

17. The number of beads is given by:

$$N = \frac{3M_0}{4\pi R_0^3 \rho_0} \quad (1)$$

18. The mass of drug per particle, m_1 , and the mass of coating per particle, m_2 , are given by:

$$m_1 = \frac{M_1}{N} \quad \text{and} \quad m_2 = \frac{M_2}{N} \quad (2)$$

19. From elementary geometry:

$$m_1 = \frac{4\pi}{3} \rho_1 [R_1^3 - R_0^3] \quad \text{and} \quad m_2 = \frac{4\pi}{3} \rho_2 [R_2^3 - R_1^3] \quad (3)$$

20. Finally the radius R_2 of the particle is given by:

$$R_2 = \left[R_0^3 + \frac{3m_1}{4\pi\rho_1} + \frac{3m_2}{4\pi\rho_2} \right]^{1/3} \quad (4)$$

where m_1 and m_2 are given by (1) and (2).

21. The specific weight of the inert carrier (Nonpareil 103) is $\rho_0 = 1580$ g/L (density = 1.58). The layer containing the drug substance is deposited by spray coating, and its specific weight ρ_1 is assumed to be equal to 1200 g/liter (density = 1.2). Similarly, the specific weight of the coating ρ_2 is assumed to be equal to 1000 g/liter (density = 1). Spray coating processes

generally lead to porous layers with low apparent density. However, the porosity has been neglected in order to calculate the minimum size of the coated granules disclosed by Ishibashi.

22. Table 1, below, shows the calculated diameters of the coated granules for Ishibashi's Examples 1, 2, 3, 3bis, 4, 4bis, 5 and 5bis. As a result, the minimum diameter in microns can be 930 microns as shown in Example 1.

23. This number, however, is artificially small because Ishibashi does not state the concentration of sucrose solution used.

24. A typical sucrose solution used at this time would be at least about 60%.

25. I did not know the Ishibashi sucrose solution, so I did not use this into the calculations. Any sucrose solution would result in a larger diameter. Thus, by using sucrose, Ishibashi's Example 1 would have a diameter greater than 930 microns.

TABLE 1

N° of example	1	2	3	3bis	4	4bis	5	5bis
Neutral beads								
M0 (Kg)	0,06	0,05	0,05	0,05	0,05	0,05	0,05	0,05
ρ (kg/m ³)	1580	1580	1580	1580	1580	1580	1580	1580
R ₀ (m)	0,00023	0,00023	0,00023	0,00023	0,00023	0,00023	0,00023	0,00023
Drug-loaded core								
M1 (Kg)	0,23	0,33	0,23	0,23	0,23	0,23	0,23	0,23
ρ_1 (kg/m ³)	1200	1200	1200	1200	1200	1200	1200	1200
Coating								
%coating	30	67	30	40	120	140	50	60
M2 (Kg)	0,087	0,2546	0,084	0,112	0,336	0,392	0,14	0,168
ρ_2 (kg/m ³)	1000	1000	1000	1000	1000	1000	1000	1000
R2 (m)	0,00046646	0,00059987	0,00049077	0,00050524	0,00059918	0,00051854	0,00051892	0,00053192
N° of example	1	2	3	3bis	4	4bis	5	5bis
(minimum diameter)	930	1203	930	1019	1200	1213	1080	1060

26. Table 2, below, shows the same calculation made with the largest nonpareil 103 available at the time. This calculation shows that the particle size of Ishibashi coated granules could have been as high as 2430 to 3230 μm .

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TABLE 2

N° of example	1	2	3	3bis	4	4bis	5	5bis
Neutral beads								
M0 (Kg)	0,06	0,05	0,05	0,05	0,05	0,05	0,05	0,05
Γ_k (kg/m ³)	1580	1580	1580	1580	1580	1580	1580	1580
R ₀ (m)	0,0006	0,0006	0,0006	0,0006	0,0006	0,0006	0,0006	0,0006
Drug-loaded core								
M1 (Kg)	0,23	0,33	0,23	0,23	0,23	0,23	0,23	0,23
Γ_k (kg/m ³)	1200	1200	1200	1200	1200	1200	1200	1200
Coating								
%coating	30	67	30	40	120	140	50	60
M2 (kg)	0,087	0,2546	0,084	0,112	0,336	0,392	0,14	0,168
Γ_k (kg/m ³)	1000	1000	1000	1000	1000	1000	1000	1000
R2 (m)	0,00348646	0,00059987	0,00049077	0,00050524	0,00059918	0,00061854	0,00051892	0,00053192
Final product								
Particle size (µm)	2300	2330	2350	2500	2150	2330	2710	2760

27. In conclusion, both Table 1 and Table 2 neglect the volume of sucrose, and hence underestimate the size of the coated granules disclosed in Ishibashi. It thus appears that the particle size of the coated granules is greater than 930 µm (if the smallest available nonpareil is used) or greater than 2430 µm (if the largest available nonpareil is used).

28. I declare that all statements made of my own knowledge are true and all statements made on information and belief are believed to be true. I make this declaration with the understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent application.



Catherine CASTAN



Date

Appendix: Handbook of Pharmaceutical Excipients, 2nd Edition

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Sugar Spheres

1. Nonsynonymous Names

USPSP: Sugar spheres

2. Synonyms

Non-pareil; Non-pareil 103; non-pareil teeth; No-Care; No-Pareil; sugar seeds.

3. Chemical Name and CAS Registry Number

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4. Empirical Formula Molecular Weight

See Section 8.

5. Structural Formula

See Section 3.

6. Functional Category

Tablet and capsule diluent.

7. Applications in Pharmaceutical Formulation or Technology

Sugar spheres are used as inert cores in capsule and tablet formulations particularly multiphase sustained release formulations.^{4,51} They form the base upon which a drug is coated, usually followed by a release modifying polymer coating. Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer, or due to the controlled erosion of the polymer coating. Complex drug mixtures contained within a single dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

Sugar spheres are also used in confectionery products.

8. Description

The USPSP XVII describes sugar spheres as approximately spherical granules of a beveled minimal disc shape with a uniform diameter and containing not less than 62.5% and not more than 71.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch. Usually white in color, sugar spheres may also contain approved coloring agents.

9. Pharmacopeial Specifications

Test	USPSP XVII
Identification (starch)	+
Specific rotation	+43° to +45°
Microbial limits	+
Loss on drying	< 4.4%
Residue on ignition	< 0.25%
Heavy metals	< 1 ppm
Particle size distribution	< 10% oversize, < 10% undersize

10. Typical properties

Particle size distribution: sugar spheres are of a uniform diameter. The following sizes are commercially available (US standard sizes):
 15-40 mesh (425-500 µm)
 30-35 mesh (500-600 µm)
 45-50 mesh (600-710 µm)
 50-60 mesh (710-850 µm)
 60-70 mesh (850-1000 µm)
 70-80 mesh (1000-1180 µm)
 80-100 mesh (1180-1600 µm)
 100-120 mesh (1250-1600 µm)
 120-150 mesh (1500-1800 µm)
 150-200 mesh (1800-2500 µm)
 200-250 mesh (2500-3000 µm)
 250-300 mesh (3000-3500 µm)
 300-350 mesh (3500-4000 µm)
 350-400 mesh (4000-4500 µm)
 400-450 mesh (4500-5000 µm)
 450-500 mesh (5000-5500 µm)
 500-550 mesh (5500-6000 µm)
 550-600 mesh (6000-6500 µm)
 600-650 mesh (6500-7000 µm)
 650-700 mesh (7000-7500 µm)
 700-750 mesh (7500-8000 µm)
 750-800 mesh (8000-8500 µm)
 800-850 mesh (8500-9000 µm)
 850-900 mesh (9000-9500 µm)
 900-950 mesh (9500-10000 µm)
 950-1000 mesh (10000-10500 µm)
 1000-1050 mesh (10500-11000 µm)
 1050-1100 mesh (11000-11500 µm)
 1100-1150 mesh (11500-12000 µm)
 1150-1200 mesh (12000-12500 µm)
 1200-1250 mesh (12500-13000 µm)
 1250-1300 mesh (13000-13500 µm)
 1300-1350 mesh (13500-14000 µm)
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 1800-1850 mesh (18500-19000 µm)
 1850-1900 mesh (19000-19500 µm)
 1900-1950 mesh (19500-20000 µm)
 1950-2000 mesh (20000-20500 µm)
 2000-2050 mesh (20500-21000 µm)
 2050-2100 mesh (21000-21500 µm)
 2100-2150 mesh (21500-22000 µm)
 2150-2200 mesh (22000-22500 µm)
 2200-2250 mesh (22500-23000 µm)
 2250-2300 mesh (23000-23500 µm)
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 2850-2900 mesh (29000-29500 µm)
 2900-2950 mesh (29500-30000 µm)
 2950-3000 mesh (30000-30500 µm)
 3000-3050 mesh (30500-31000 µm)
 3050-3100 mesh (31000-31500 µm)
 3100-3150 mesh (31500-32000 µm)
 3150-3200 mesh (32000-32500 µm)
 3200-3250 mesh (32500-33000 µm)
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 14250-14300 mesh (143000-143500 µm)
 14300-14350 mesh (143500-144000 µm)
 14350-14400 mesh (144000-144500 µm)
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 14500-14550 mesh (145500-146000 µm)
 14550-14600 mesh (146000-146500 µm)
 14600-14650 mesh (146500-147000 µm)
 14650-14700 mesh (147000-147500 µm)
 14700-14750 mesh (147500-148000 µm)
 14750-14800 mesh (148000-148500 µm)
 14800-14850 mesh (148500-149000 µm)
 14850-14900 mesh (149000-149500 µm)
 14900-14950 mesh (149500-150000 µm)
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 16000-16050 mesh (160500-161000 µm)
 16050-16100 mesh (161000-161500 µm)
 16100-16150 mesh (161500-162000 µm)
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 16350-16400 mesh (164000-164500 µm)
 16400-16450 mesh (164500-165000 µm)
 16450-16500 mesh (165000-165500 µm)
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 16600-16650 mesh (166500-167000 µm)
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 16700-16750 mesh (167500-168000 µm)
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 16800-16850 mesh (168500-169000 µm)
 16850-16900 mesh (169000-169500 µm)
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 16950-17000 mesh (170000-170500 µm)
 17000-17050 mesh (170500-171000 µm)
 17

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SAR Sugar Spheres

Sugar Spheres

1. Nonproprietary Names

USP: Sugar spheres

2. Synonyms

Non-pareil, Non-pareil 603, non-pareil beads, No-Care, No-Pareil, sugar beads.

3. Chemical Name and CAS Registry Number

—

4. Empirical Formula Molecular Weight

See Section 8.

5. Structural Formula

See Section 8.

6. Functional Category

Tablet and capsule diluent.

7. Applications in Pharmaceutical Formulation or Technology

Sugar spheres are used as inert cores for capsule and tablet formulations, particularly multiparticulate sustained-release formulations (4). They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating. Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer or due to the controlled erosion of the polymer coating. Composite drug mixtures contained within a single dosage form may be prepared by coating the drug with different batches of sugar spheres with different protective polymer coatings.

Sugar spheres are also used in confectionery products.

8. Description

The USP describes sugar spheres as approximately spherical granules of a labelled nominal size range with a uniform diameter and containing not less than 63.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch. Usually white in color, sugar spheres may also contain approved coloring agents.

15. Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled.

16. Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in the Approved Medicines list in the UK and Europe. The sucrose and starch components of sugar spheres are individually approved for use as food additives in Europe and the US.

17. Pharmacopeias

US.

18. Related Substances

Compressible sugar; confectioner's sugar; starch; sucrose.

9. Pharmacopeial Specifications

Test	USP
Identification	+
Specific rotation	+11° to +14°
Microbial limits	+
Loss on drying	≤ 4.0%
Residue on ignition	≤ 0.25%
Heavy metals	≤ 5 ppm
Particle size distribution	+
Organic volatile impurities	+
Sucrose (total basis)	62.3-91.5%

10. Typical properties

Particle size distribution: sugar spheres are of a uniform diameter. The following sizes are commercially available:

(US standard sieves)	
15-40 mesh (420-500 µm)	
15-18 mesh (500-590 µm)	
25-30 mesh (590-710 µm)	
20-25 mesh (710-840 µm)	
18-20 mesh (840-1000 µm)	
16-20 mesh (840-1100 µm)	
14-18 mesh (1000-1410 µm)	

Solubility: solubility in water varies according to the sucrose in starch ratio. The sucrose component is freely soluble in water whereas the starch component is insoluble in cold water.

11. Stability and Storage Conditions

Sugar spheres are stable when stored in a well-closed container in a cool, dry place.

12. Incompatibilities

See Starch and Sucrose for information concerning the incompatibilities of the component materials of sugar spheres.

13. Method of Manufacture

Sugar spheres are prepared from crystalline sucrose which is coated using sugar syrup and a starch-binding powder.

14. Safety

Sugar spheres are used in oral pharmaceutical formulations. The sucrose and starch components of sugar spheres are widely used in edible food products and oral pharmaceutical formulations.

The adverse reactions and precautions necessary with the starch and sucrose components should be considered in any product containing sugar spheres. For example, sucrose is generally regarded as more cariogenic than other carbohydrates and is higher doses is also contraindicated in diabetic patients.

See Starch and Sucrose for further information.

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19. Comments

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20. Specific References

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22. Authors

RC Monahan